Int. J. Cancer: **121,** 1346–1351 (2007)

Alcohol and folate consumption and risk of benign proliferative epithelial disorders of the breast

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Alcohol consumption has been associated with increased breast cancer risk and the increase in risk may be attenuated by adequate folate intake. However, their associations with the risk of benign proliferative epithelial disorders (BPEDs) of the breast, possible precursors of breast cancer, are not well understood. To investigate these associations, we conducted a cohort study among 68,132 postmenopausal women participating in the Women's Health Initiative randomized clinical trials. Women were prospectively followed and those reporting a breast procedure (open surgical biopsy or core needle biopsy) had histological sections obtained for central pathology review. A total of 1,792 women with BPED of the breast were identified over an average of 7.8 years of follow-up. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence limits (CLs) for the associations of interest. Compared to nondrinkers, total current alcohol intake of 30 g/day or more was not associated with BPED risk (HR = 0.98, 95% CL = 0.70, 1.38). The risk of BPED was not associated with folate intake from diet (highest *vs.* lowest quartile: HR = 1.10, 95% CL = 0.96, 1.26), from supplements (yes *vs.* no: HR = 1.05, 95% CL = 0.96, 1.16) or from all sources combined (highest *vs.* lowest quartile: HR = 1.11, 95% CL = 0.96, 1.27). Furthermore, there was no effect modification between alcohol and folate in relation to the risk of BPED. In conclusion, we observed that alcohol consumption and folate intake were not associated with altered risk of BPED, and that there was no effect modification between them in relation to the risk of BPED.

Key words: alcohol; folate; risk; benign proliferative epithelial disorders of the breast; Women's Health Initiative

Alcohol consumption has been consistently and positively associated with increased breast cancer risk,[1,2] and it is hypothesized that this association is mediated by circulating estrogens and subsequently epithelial cell proliferation.[3,4] This mechanism suggests that alcohol may also increase the risk of benign proliferative epithelial disorders (BPEDs) of the breast, conditions which are possible precursors of breast cancer.[5] However, previous studies of alcohol consumption and BPED risk have been inconsistent, with null, positive and inverse associations observed.[6–9]

Folate is essential for normal DNA synthesis, repair and methylation.[10] Although recent meta-analyses found no consistent support for an overall relationship between folate intake and breast cancer risk,[11,12] some observational studies have shown that adequate folate intake may attenuate the increased breast cancer risk in association with moderate or heavy alcohol consumption.[13–16] The interdependence of alcohol and folate must be considered when evaluating the effect of alcohol consumption on breast cancer risk and is potentially relevant to studies of BPED as well. However, no published studies have investigated the effect of folate on BPED risk and the few studies on alcohol consumption and BPED risk were not stratified on folate intake.[6–9]

To address this issue, we examined the main and joint effects of alcohol consumption and folate intake on the risk of BPED of the breast in a cohort study undertaken in postmenopausal women participating in the Women's Health Initiative (WHI) randomized clinical trials.

Material and methods

Study population

The WHI randomized clinical trials consist of several overlapping components including 2 postmenopausal hormone trials, a dietary modification trial and a calcium–vitamin D supplementation trial. Participants in the calcium–vitamin D supplementation trial were enrolled from those women who were either in the postmenopausal hormone trials or in the dietary modification trial, or both. The trials were conducted among 68,132 postmenopausal women aged 50–79 at enrollment and randomized between 1993 and 1998 in 40 clinics across the United States. The study design, implementation and characteristics of the study populations have been described in detail elsewhere.[17–20] Women in the postmenopausal hormone trials underwent annual clinical breast exams and mammograms, whereas women in the dietary modification trial underwent biennial mammograms.

Case ascertainment

Every 6 months, participants in the trial completed medical questionnaires on clinical events including breast procedures (open surgical biopsy or core needle biopsy). Medical record and pathology reports were routinely collected for women reporting either invasive or noninvasive breast cancer diagnosis. In the study reported here, women who had undergone a breast procedure were asked to provide consent for retrieval of the histological sections resulting from the procedures and the sections then underwent centralized histological review. As of September 2005, 4,531 surgical or core needle biopsies had been performed among the trial participants, and consent from participants had been obtained for 4,325 biopsies (some participants had more than 1 biopsy). Among those 4,325 biopsies, 4,225 histological sections were obtained and reviewed by the study pathologist. The study was approved by the appropriate Institutional Review Boards, and informed consent was obtained from all study participants.

Histopathology

The histological sections were reviewed blinded to randomization assignment in the clinical trials and other exposure information. They were classified on the presence of benign epithelial pro-

Grant sponsor: NIH; Grant number: RO1-CA77290
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Received 4 January 2007; Accepted after revision 11 April 2007
DOI 10.1002/ijc.22861
Published online 29 May 2007 in Wiley InterScience (www.interscience.wiley.com).

liferation and the presence of atypia in those with a BPED using a previously described approach.[21] For participants who had multiple biopsies during the follow-up period, the earliest biopsy with a diagnosis of BPED of the breast was used as the end-point of interest and any biopsies performed afterwards were not taken into consideration. In addition, histological sections were evaluated for the presence of fibroadenoma, sclerosing adenosis and micropapilloma.

Case definition

Cases were defined as women with an incident BPED of the breast that arose during follow-up. As of September 2005, a total of 1,792 incident cases of BPED had been identified among the trial participants after an average of 7.8 years of follow-up. The cases were categorized into 2 groups: women with non-atypical epithelial proliferation (BPED without atypia) and women with atypical hyperplasia (BPED with atypia). Of the 1,792 cases, 294 had atypical hyperplasia and 1,498 had a non-atypical form of BPED of the breast.

Exposure assessment

Upon enrollment, all WHI clinical trial participants provided questionnaire information on demographic characteristics, personal habits, reproductive history, hormone use, medical history, family history, dietary and supplemental intake and alcohol intake. Women who had 12 alcohol drinks during their entire life were asked whether they were still drinking. Nondrinkers were defined as women with less then 12 drinks of any kind of alcohol in their entire life and former drinkers were defined as women who had ever had $\geq$12 alcoholic beverages in their life but were not still drinking. The frequency of alcohol consumption and the associated serving sizes for current drinkers were recorded in the food frequency questionnaire (FFQ), from which daily alcohol consumption amount was estimated.

The FFQ sought frequency and serving size of 122 foods consumed over the past 3 months at recruitment.[22] The daily nutrient (including folate) intake from a given food was calculated by multiplying its portion size by the number of servings per day and its nutrient content. The daily nutrient intake for each study subject was then calculated by summing across all food items. The nutrient content values were derived from the University of Minnesota Nutrition Coding Center nutrient database (Nutrition Coordinating Center, Minneapolis, MN).[23] In addition, intakes of multiple vitamins and single supplements were collected at baseline, from which supplemental folic acid intake was estimated.

Statistical analysis

Cox proportional hazards models (using time-on-study as the time scale) were used to estimate hazard ratios (HRs) and 95% confidence limits (CLs) for the associations of BPED with alcohol consumption and folate intake. Cases contributed person-time to the study from their date of enrollment until the date of BPED diagnosis, and noncases (participants who were censored) contributed person-time from their date of enrollment until the end of follow-up, date of death, date of withdrawal from the study or date of ceasing to be at risk of developing BPED (*e.g.*, due to the development of breast cancer or due to a bilateral prophylactic mastectomy), whichever came first. Alcohol intake was analyzed from all sources combined, and from beer, wine and liquor, separately. The basic unit of alcohol intake was grams of ethanol consumed per day. The conversion factors were 12.80, 10.97 and 13.00 g of ethanol for 12 ounces of beer, 4 ounces of wine and 1.5 ounces of liquor, respectively. In categorical analyses, alcohol consumption was classified into 5 groups consisting of nondrinkers, former-drinkers and current drinkers who drank less than 15, 15 to <30 and 30 g or more per day. Similarly, folate intake was analyzed from all sources combined, and from diet and supplements separately. Total folate intake was assessed either by summing up total micrograms of folate consumed per day (μg/day) from dietary and supplemental sources or by summing up dietary folate equivalents from diet and supplements consumed per day. One dietary folate equivalent corresponds to 1 μg of natural food folate and 0.6 μg of folic acid from supplements or fortified foods.[24] Dietary and supplemental folate intake was adjusted for energy intake using the residual method.[25] Participants with estimated energy intake less than 600 or more than 5,000 calories per day were excluded from analyses because their energy intake estimates suggested that they did not complete the FFQ appropriately. Quartile analyses were used to assess daily folate intake in association with risk of BPED of the breast; the quartile cut-off points were determined using the distribution of folate intake in the total population. Using micrograms of folate intake and dietary folate equivalents yielded similar results. Therefore, only the results obtained using micrograms of folate intake are shown.

In multivariate analyses, we controlled for energy intake, age at recruitment (continuous), ethnicity (non-Hispanic White, Black/African American, Hispanic/Latino and other ethnic groups), region of residence (Northeast, South, West and Midwest), randomization assignment (18 categories), frequency of breast exams during follow-up period (continuous) and frequency of mammograms during follow-up period (continuous). We further controlled for age (years) at menarche (<12, 12, 13, 14+), age (years) at menopause (<46, 46–50, 51–55, 56+, with a separate category for missing), number of live births (0, 1–2, 3–4, 5+), years of oral contraceptive use (0, >0–1, >1–4, >4–8, >8), years of postmenopausal hormone use (0, >0 to <5, 5 to <10, 10 to <15, 15+), body mass index (BMI) (continuous) and family history of breast cancer (yes or no, with a separate category for missing) to assess potential confounding effects by these factors.

For tests of trend in risk across successive levels of categorical variables, we assigned the categories their ordinal number and then fitted the resulting variable as a continuous variable in the risk models. We then evaluated the statistical significance of the corresponding coefficient using the Wald test.[26] The joint effects of alcohol and folate intake on the risk of BPED were assessed by first cross-classifying the study population into multiple categories according to levels of alcohol and folate intake, and then comparing subjects in different categories with a common reference group consisting of subjects who were nondrinkers and who con-

TABLE I – ASSOCIATION BETWEEN TOTAL ALCOHOL CONSUMPTION AND RISK OF BPED OF THE BREAST

Alcohol (g/day)	No. of cases	Person-years of follow-up	HR (95% CL)	
			Model 1[1]	Model 2[2]
Never drinkers	165	55,636	1.0	1.0
Former drinkers	291	96,434	1.03 (0.85, 1.25)	1.02 (0.84, 1.24)
Current drinkers				
>0 to <15	1,148	317,732	1.16 (0.98, 1.38)	1.11 (0.94, 1.32)
15 to <30	111	34,034	1.09 (0.85, 1.39)	1.02 (0.79, 1.30)
30+	44	15,386	0.98 (0.70, 1.38)	0.89 (0.63, 1.26)
			$p_{trend} = 0.90$	$p_{trend} = 0.60$

[1]Adjusted for energy intake, age at recruitment, ethnicity, region of residence, randomization assignment, frequency of physical exams and frequency of mammograms.–[2]Adjusted for covariates in model 1 and the following variables: age at menarche, age at menopause, number of live births, duration of oral contraceptive use, duration of postmenopausal hormone use, BMI and family history of breast cancer.

TABLE II – ASSOCIATION BETWEEN TOTAL ALCOHOL CONSUMPTION AND RISK OF BPED STRATIFIED BY HISTOLOGICAL TYPE OF BPED

Alcohol (g/day)	Non-atypical BPED			Atypical hyperplasia		
	No. of cases	HR (95% CL) Model 1[1]	HR (95% CL) Model 2[2]	No. of cases	HR (95% CL) Model 1[1]	HR (95% CL) Model 2[2]
Never drinkers	141	1.0	1.0	24	1.0	1.0
Former drinkers	251	1.04 (0.84, 1.28)	1.03 (0.83, 1.27)	40	0.99 (0.59, 1.67)	0.97 (0.58, 1.65)
Current drinkers						
>0 to <15	950	1.13 (0.94, 1.36)	1.08 (0.90, 1.30)	198	1.38 (0.88, 2.16)	1.32 (0.84, 2.07)
15 to <30	90	1.03 (0.79, 1.36)	0.96 (0.73, 1.27)	21	1.41 (0.77, 2.60)	1.34 (0.72, 2.46)
30+	36	0.94 (0.65, 1.36)	0.87 (0.60, 1.27)	8	1.26 (0.56, 2.86)	1.05 (0.44, 2.50)
		$p_{trend} = 0.88$	$p_{trend} = 0.49$		$p_{trend} = 0.52$	$p_{trend} = 0.80$

[1]Adjusted for energy intake, age at recruitment, ethnicity, region of residence, randomization assignment, frequency of physical exams and frequency of mammograms.–[2]Adjusted for covariates in model 1 and the following variables: age at menarche, age at menopause, number of live births, duration of oral contraceptive use, duration of postmenopausal hormone use, BMI and family history of breast cancer.

TABLE III – ASSOCIATION BETWEEN DAILY FOLATE INTAKE AND RISK OF BPED OF THE BREAST

Folate	Level	No. of cases	Person-years	HR (95% CL)	
				Model 1[1]	Model 2[2]
All sources (μg/day)	0–351	412	130,668	1.0	1.0
	>351–456	452	130,890	1.11 (0.97, 1.27)	1.09 (0.95, 1.25)
	>456–748	467	129,417	1.18 (1.03, 1.35)	1.13 (0.99, 1.29)
	>748	433	128,846	1.11 (0.96, 1.27)	1.04 (0.91, 1.20)
				$p_{trend} = 0.098$	$p_{trend} = 0.46$
Diet (μg/day)	0–320	422	129,664	1.0	1.0
	>320–371	453	127,801	1.08 (0.95, 1.24)	1.08 (0.94, 1.23)
	>371–430	454	131,376	1.08 (0.94, 1.23)	1.07 (0.93, 1.22)
	>430	435	130,978	1.10 (0.96, 1.26)	1.09 (0.95, 1.25)
				$p_{trend} = 0.20$	$p_{trend} = 0.27$
Supplements	No	1,017	306,624	1.0	1.0
	Yes[3]	747	213,176	1.05 (0.96, 1.16)	1.00 (0.91, 1.11)

[1]Adjusted for energy intake, age at recruitment, ethnicity, region of residence, randomization assignment, frequency of physical exams and frequency of mammograms.–[2]Adjusted for covariates in model 1 and the following variables: age at menarche, age at menopause, number of live births, duration of oral contraceptive use, duration of postmenopausal hormone use, BMI and family history of breast cancer.–[3]A majority (76%) of subjects took 400 μg of supplemental folic acid per day.

sumed high levels of folate (>median intake). Tests for interaction were based on the likelihood ratio test comparing models with or without cross-classification of the variables of interest. The likelihood ratio test was conducted by referring 2* the absolute difference in the log likelihoods of the 2 models to the X^2 distribution on degrees of freedom equal to the difference in the number of covariates of the 2 models. To explore etiological differences between non-atypical BPED and atypical hyperplasia, we investigated their associations with alcohol and folate intake separately. All statistical analyses were performed in SAS 9.1 (SAS Institute, Cary, NC). *p*-values were two-sided.

Results

We identified 1,792 incident cases of BPED of the breast (294 with atypia and 1,498 without atypia) over an average of 7.8 years of follow-up. In comparison with noncases, cases were younger, and were more likely to reside in the Midwest, to be non-Hispanic White, to have a BMI less than 30 kg/m^2, to have a family history of breast cancer, to have used oral contraceptives and postmenopausal hormones for a longer period and to have had fewer live births (data not shown). In addition, cases and noncases had similar annual frequencies of breast exams and mammograms.

Among the 67,592 study participants with alcohol intake data, 10% were nondrinkers, 19% were former drinkers and 71% were current drinkers. Overall, there was no association between alcohol drinking status (former *vs.* never: HR = 1.03, 95% CL = 0.85, 1.26; current *vs.* never: HR = 1.15, 95% CL = 0.97, 1.36) and risk of BPED of the breast. In comparison with nondrinkers, total current alcohol intake was not associated with risk of BPED of the breast (30+ *vs.* 0 g/day: HR = 0.98, 95% CL = 0.70, 1.38, p_{trend} = 0.90) (Table I). In addition, we observed no association between risk of BPED and alcohol consumption by beverage type (data not shown). Furthermore, we observed little association of total alcohol consumption with non-atypical BPED and atypical hyperplasia, although our analysis of atypical hyperplasia was limited by a relatively small number of cases at the higher levels of intake (Table II).

The mean dietary folate intake was 380 (SD = 89) and 384 (SD = 100) μg/day for cases of BPED and noncases, respectively. Approximately 40% of study participants took supplemental folic acid regularly, mostly (76% of these subjects) at a dose of 400 μg/day. The estimated median folate intake from all sources combined was 462 (interquartile range = 390) and 456 (interquartile range = 398) μg/day for cases of BPED and noncases, respectively. Table III summarizes the association between folate intake and risk of BPED of the breast. Overall, risk of BPED of the breast was not associated with folate intake from all sources combined or with folate intake from diet and supplements, separately. Furthermore, no associations between folate intake and risks of non-atypical BPED and atypical hyperplasia were demonstrated (Table IV). In addition, decile analyses revealed no altered risk of BPED of the breast when comparing women with the highest decile level of folate intake to those with the lowest decile level of intake (for total folate intake, HR = 1.08, 95% CL = 0.86, 1.35).

The joint effects of alcohol and folate intake on the risk of BPED overall and by its histological subtypes are summarized in Tables V and VI. In comparison with subjects who were nondrinkers and whose folate consumption was relatively high (>median), subjects who consumed ≥30 g/day of alcohol and whose folate consumption was relatively low (at or below the median) experienced no increased risk of BPED of the breast overall or of non-atypical BPED. However, our power to assess the joint effect of alcohol and folate intake on the risk of atypical

TABLE IV – ASSOCIATION BETWEEN DAILY FOLATE INTAKE AND RISK OF BPED STRATIFIED BY HISTOLOGICAL TYPE OF BPED

Total folate intake (μg/day)	Non-atypical BPED			Atypical hyperplasia		
	No. of cases	HR (95% CL) Model 1[1]	HR (95% CL) Model 2[2]	No. of cases	HR (95% CL) Model 1[1]	HR (95% CL) Model 2[2]
0–351	350	1.0	1.0	62	1.0	1.0
>351–456	367	1.06 (0.91, 1.23)	1.04 (0.90, 1.20)	85	1.41 (1.02, 1.96)	1.38 (0.99, 1.92)
>456–748	404	1.20 (1.04, 1.39)	1.15 (0.99, 1.33)	63	1.06 (0.75, 1.51)	1.03 (0.72, 1.48)
>748	352	1.06 (0.91, 1.23)	1.00 (0.86, 1.16)	81	1.38 (0.99, 1.94)	1.32 (0.94, 1.86)
		$p_{trend} = 0.21$	$p_{trend} = 0.71$		$p_{trend} = 0.21$	$p_{trend} = 0.33$

[1]Adjusted for energy intake, age at recruitment, ethnicity, region of residence, randomization assignment, frequency of physical exams and frequency of mammograms.–[2]Adjusted for covariates in model 1 and the following variables: age at menarche, age at menopause, number of live births, duration of oral contraceptive use, duration of postmenopausal hormone use, BMI and family history of breast cancer.

TABLE V – JOINT EFFECTS OF ALCOHOL AND FOLATE INTAKE ON THE RISK OF BPED

Total alcohol intake (g/day)	Total folate intake	No. of cases	Person-years	HR (95% CL)	
				Model 1[1]	Model 2[2]
Never drinkers	>median	72	24,403	1.0	1.0
Former drinkers	>median	129	45,990	0.95 (0.71, 1.28)	0.96 (0.71, 1.28)
Current drinkers					
>0 to <15	>median	621	162,045	1.25 (0.98, 1.60)	1.21 (0.94, 1.55)
15 to <30	>median	56	16,727	1.13 (0.79, 1.61)	1.06 (0.74, 1.51)
30+	>median	17	6,908	0.84 (0.49, 1.43)	0.76 (0.44, 1.32)
Never drinkers	≤median	88	29,522	0.99 (0.73, 1.36)	1.04 (0.76, 1.43)
Former drinkers	≤median	159	48,187	1.10 (0.83, 1.45)	1.13 (0.85, 1.50)
Current drinkers					
>0 to <15	≤median	527	155,687	1.07 (0.83, 1.37)	1.07 (0.83, 1.38)
15 to <30	≤median	55	17,307	1.04 (0.73, 1.49)	1.03 (0.72, 1.47)
30+	≤median	27	8,478	1.09 (0.70, 1.70)	1.05 (0.66, 1.65)
				$p_{interaction} = 0.16$	$p_{interaction} = 0.19$

[1]Adjusted for energy intake, age at recruitment, ethnicity, region of residence, randomization assignment, frequency of physical exams and frequency of mammograms.–[2]Adjusted for covariates in model 1 and the following variables: age at menarche, age at menopause, number of live births, duration of oral contraceptive use, duration of postmenopausal hormone use, BMI and family history of breast cancer.

TABLE VI – JOINT EFFECTS OF ALCOHOL AND FOLATE INTAKE ON THE RISK OF NON-ATYPICAL BPED AND ATYPICAL HYPERPLASIA

Total alcohol intake (g/day)	Total folate intake	Non-atypical BPED			Atypical hyperplasia		
		No. of cases	HR (95% CL) Model 1[1]	HR (95% CL) Model 2[2]	No. of cases	HR (95% CL) Model 1[1]	HR (95% CL) Model 2[2]
Never drinkers	>median	61	1.0	1.0	11	1.0	1.0
Former drinkers	>median	114	1.01 (0.74, 1.38)	1.01 (0.74, 1.38)	15	0.69 (0.32, 1.50)	0.69 (0.32,1.50)
Current drinkers							
>0 to <15	>median	516	1.24 (0.95, 1.63)	1.20 (0.91, 1.58)	105	1.30 (0.69, 2.43)	1.23 (0.65, 2.30)
15 to <30	>median	47	1.13 (0.77, 1.67)	1.06 (0.72, 1.57)	9	1.11 (0.46, 2.71)	1.04 (0.43, 2.53)
30+	>median	14	0.82 (0.46, 1.47)	0.74 (0.40, 1.35)	3	0.95 (0.26, 3.42)	0.90 (0.25, 2.27)
Never drinkers	≤median	77	1.03 (0.73, 1.44)	1.09 (0.77, 1.53)	11	0.81 (0.35, 1.86)	0.82 (0.35, 1.89)
Former drinkers	≤median	134	1.10 (0.81, 1.50)	1.14 (0.84, 1.56)	25	1.07 (0.52, 2.18)	1.05 (0.51, 2.16)
Current drinkers							
>0 to <15	≤median	434	1.05 (0.80, 1.38)	1.06 (0.80, 1.40)	93	1.16 (0.62, 2.18)	1.14 (0.61, 2.15)
15 to <30	≤median	43	0.98 (0.66, 1.45)	0.96 (0.65, 1.43)	12	1.40 (0.61, 3.19)	1.35 (0.59, 3.10)
30+	≤median	22	1.06 (0.65, 1.73)	1.06 (0.65, 1.73)	5	1.26 (0.44, 3.66)	0.98 (0.31, 3.10)
			$p_{interaction} = 0.29$	$p_{interaction} = 0.26$		$p_{interaction} = 0.53$	$p_{interaction} = 0.64$

[1]Adjusted for energy intake, age at recruitment, ethnicity, region of residence, randomization assignment, frequency of physical exams and frequency of mammograms.–[2]Adjusted for covariates in model 1 and the following variables: age at menarche, age at menopause, number of live births, duration of oral contraceptive use, duration of postmenopausal hormone use, BMI and family history of breast cancer.

hyperplasia was limited by the small number of cases of atypical hyperplasia.

Discussion

Epidemiological studies have suggested that alcohol consumption is associated with an increased risk of breast cancer and the risk can be attenuated by an adequate intake of folate.[13–16,27,28] We hypothesized that the same relationship would be relevant to BPED of the breast, possible precursors of breast cancer.[5] However, our results do not support an increased risk of BPED of the breast in association with high alcohol consumption or low folate intake and provide no evidence for variation in the association between alcohol consumption and BPED risk by levels of folate intake. The null association between alcohol consumption and risk of BPED of the breast was uniform across different beverage types. Similarly, the null association between folate intake and risk of BPED of the breast was uniform across folate intake from different sources. Furthermore, the study results were similar after exclusion of BPED cases diagnosed within 1 year of recruitment, after exclusion of study participants with self-report of prior benign breast biopsies at baseline and after using dietary folate equivalents as the basic unit of folate intake to account for differences in the bioavailability of natural folate and folic acid from

supplements and fortified foods.[10] A large fraction of study participants were randomized in 1 or more of the intervention studies. When analyses were restricted to participants who received no interventions (n = 26,515), the results were similar to those presented here, indicating no effect-modification by the interventions.

To date, 4 epidemiological studies have assessed the relationship between alcohol consumption and risk of BPED of the breast. Both a case–control study of predominantly premenopausal women and a nested case–control study of predominantly postmenopausal women observed no associations of BPED with alcohol consumption.[6,7] The Nurses' Health Study II found that risk of BPED was positively associated with alcohol consumption between the ages of 18 and 22, but no associations were detected for recent alcohol consumption or for consumption between the ages of 15 and 17.[8] The Canadian National Breast Screening Study associated alcohol consumption with a non-dose-dependent reduction in risk of BPED.[9] Notably, none of these studies assessed the association between alcohol consumption and risk of BPED after stratification by folate intake levels. In addition, no studies have been published investigating the effect of folate intake on the risk of BPED.

On average, postmenopausal women in our study consumed ~384 μg of dietary folate per day. About 40% of these women took supplemental folic acid regularly. The estimated median folate intake from all sources was 456 μg/day (interquartile range = 398 μg/day). Notably, dietary and total folate intakes were much higher than in studies that have investigated the interaction of alcohol and folate intake on breast cancer risk.[13–16] High folate intake in our study population is likely partially due to folic acid-fortified cereals and grain products, which are widely consumed in the United States.[29] In addition, alcohol consumption was relatively low in our study population with less than 10% of women consuming >15 g/day of alcohol at baseline. In contrast, studies which observed an interaction between alcohol and folic intake on breast cancer incidence were generally conducted among subjects with relatively low folate intake, relatively high alcohol consumption or both. For example, Baglietto *et al*.[13] observed an increased risk of breast cancer in association with a 40 g/day increment of alcohol consumption (OR = 2.00, 95% CL = 1.14, 3.49) but only among women who had low folate intake (mean = 200 μg/day). In contrast, the mean dietary folate intake in our lowest intake group (first quartile) was 278 μg/day. Thus, our null findings could be due to the fact that alcohol consumption in this population was too low and folate intake was too high to observe effects of alcohol and folate on risk of BPED of the breast. The findings may also suggest that joint influence of alcohol and folate on breast cancer risk occurs downstream of lesions identified as BPED of the breast, although interpretation of the results on atypical hyperplasia should be cautious given the small sample size.

Study limitations include the recognized potential for measurement error in the exposures of interest using FFQs[30] and absence of lifetime history of alcohol consumption, preventing examination of risk of BPED at various ages. Study strengths include the large sample size, the prospective study design, essentially complete follow-up of the cohort, comprehensive baseline data and centralized histological review. The frequent breast exams and mammograms should have minimized selection bias and, to control for potential confounding, we adjusted for a wide range of potential BPED risk factors in multivariate analyses.

In conclusion, we observed that alcohol consumption and folate intake were not associated with altered risk of BPED of the breast, and that there was no effect modification between them in relation to the risk of BPED.

Acknowledgements

The WHI program is funded by the National Heart, Lung and Blood Institute, U.S. Department of Health and Human Services. We are indebted to the participants and investigators in the WHI Clinical Trial. We also thank Mindy Ginsberg and Mary Pettinger for managing the datasets.

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